

REMARKS

Claims 1-45 are pending in this application. Claims 16, 17, 25, 26, 31-40, 43 and 44 have been withdrawn from consideration. Applicants reiterate their request for rejoinder of dependent method claims 35-40, 43 and 44.

Double Patenting

Claims 1-15, 18-24, 27-30, 41 and 45 were provisionally rejected over the claims of co-pending USSN 10/584,382. Applicants request that this provisional rejection be held in abeyance until the claims are otherwise allowable, at which time it will be addressed

Rejections Under 35 U.S.C. § 103

Rejection for Alleged Obviousness Over Eriksen

Claims 1, 4-15, 18, 19, 27-30 and 42 were rejected for alleged obviousness over Eriksen et al US 2004/0146462 (“Eriksen”). While the Examiner concedes that Eriksen does not disclose a supermolecular structure having a particle size of 100 nm or lower, she finds that it would have been obvious to use an emulsion component with “a particle size around 100 nm” and that a skilled person would have an expectation of success “because Eriksen teaches that emulsion particles may be as small as 0.1 micron in order to facilitate unimpeded passage through the pulmonary system.”

Applicants respectfully traverse. Eriksen relates to a preparation comprising a first component in the form of gas-filled microvesicles and a second component in the form of an oil-in-water emulsion to be associated with the first component. Association between the two components can be achieved in many ways, including electrostatic binding (see par. 28).

Concerning the second component, contrary to Examiner’s statement on page 8, 4th line of the OA, Eriksen does not disclose droplets as small as 100 nm. Cited paragraph 46 of Eriksen recites in fact: “droplet size shall preferably be … greater than 0.1 μ m”, which excludes the instantly claimed upper limit of 100 nm. Eriksen then mentions that it may be advantageous to employ microbubbles and droplets of substantially similar size, i.e. 1-7 μ m. Thus, Eriksen is directed to use of relatively large emulsion droplets which may approach the size of the gas-filled microvesicles.

In contrast, the present invention requires that the supermolecular structure formed by the second component is smaller than the gas-filled microvesicles and is 100 nm or less. The advantages of such small components are explained on page 29, lines 8-18 of the application as filed:

As it can be appreciated, because of the relatively smaller dimensions of the MAC with respect to the gas-filled microvesicle, it is possible to associate a relatively large amount of MACs to the microvesicles, thus increasing the effectiveness of the assembly in terms of a higher number of binding targeting moieties and/or of the amount of releasable therapeutic or diagnostic agent incorporated therein. In addition, said relatively small dimensions of the MAC allow to obtain assemblies with dimensions comparable to the dimensions of the microvesicles. It is in fact preferred that the mean diameter in number of an assembly according to the invention is not higher than about 30% the mean diameter of the microvesicle measured before the assembling, more preferably not higher than 20% and much more preferably not higher than 10%.

Eriksen neither teaches nor suggests the use of a small second component or the advantages such structure provides. Contrary to the Examiner's suggestion, the skilled artisan would not be motivated to use emulsion droplets of less than 100nm. First of all, this would go against the specific teachings of Eriksen, as discussed above. Furthermore, use of emulsion droplets of less than 100nm would render the Eriksen compositions unfit for their purpose. Indeed, the droplets in Eriksen's emulsion are designed to provide a reservoir of diffusible gas, for the microvesicles with which they are associated. Droplets of too small dimensions (i.e. 100 nm or less) would be unsuitable for this application, as they would be unable to provide a necessary minimum volume of diffusible component to diffuse inside the microvesicle. On the other hand, the advantages illustrated above of combining MACs with small dimensions in the assembly of the invention (particularly the possibility of binding a higher number of active components associated with the microvesicle) were neither foreseeable nor derivable from the disclosure of Eriksen. Thus, Applicants submit that claims 1, 4-15, 18, 19, 27-30 and 42 are not obvious over Eriksen and request withdrawal of this rejection.

Rejection for Alleged Obviousness Over Schneider in view of Eriksen and Unger

Claims 1-15, 18-24, 27-30, 41 and 42 were rejected for alleged obviousness over Schneider et al US 6, 258,378 ("Schneider") in view of Eriksen and further in view of Unger US 2002/0159952

(“Unger”). Although the examiner concedes that Schneider does not teach that microvesicles are associated with liposomes by electrostatic interaction, the Examiner submits that “one would have been motivated to provide electrostatic interaction between the microbubble and liposome charged components since it is known in the art from Eriksen that a dispersed gas component and another phospholipid stabilized vesicle (emulsion) may have affinity for each other as a result of attractive electrostatic or other physical forces or of chemical (including biological) binding, and that inclusion of oppositely charged components may provide increased interaction and stability between the components.” OA at p. 13.

Applicants respectfully traverse. To establish a *prima facie* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or within the ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references, when combined, must teach or suggest all the claim elements. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant’s disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

With regard to the Supreme Court’s decision in *KSR Int’l. Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007), it is noted that the Court did not dismiss the usefulness the well-established “teaching, suggestion, or motivation” test set forth above, but merely cautioned against its rigid application. The Supreme Court in *KSR* commented that the Federal Circuit “no doubt has applied the test in accord with these principles [set forth in *KSR*] in many cases.” *Id.* at 419. However, the Supreme Court also opined that “[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. . . .” *Id.* Regardless of the precise test used, the Court, quoting *In re Kahn*, cautioned that “[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *Id.* at 418.

Based on the foregoing discussion, Applicant respectfully submits that the Examiner has failed to support a conclusion that the claims are *prima facie* obvious both because the references are not properly

combinable and because the combined references fail to teach or suggest each element of the claimed invention.

The Cited References are Not Properly Combined

In this regard, Applicant submits that there is no teaching or suggestion to modify Schneider in the manner proffered by the Examiner. Schneider relates to the combined use of gas-filled microvesicles and of liposomes, which Schneider defines as: *"As universally admitted, liposome solutions are aqueous suspensions of microscopic, spherically shaped, vesicles whose core may hold entrapped aqueous solutions of substances dissolved in the liposome carrier liquid. [...] Bioactive substances can be encapsulated within the aqueous phase of the core of liposome vesicles [...]"*. See col. 3, lines 40-52). The two components can be simply admixed together or "more or less" closely associated to each other. Schneider does not teach an assembly formed by the association of a microvesicle with a component, said association being effected by electrostatically binding the microvesicle with components of opposite charges.

Eriksen relates to a preparation comprising a first component in the form of gas-filled microvesicles and a second component in the form of an oil-in-water emulsion to be associated to the first component. The oil phase of the second composition comprises a diffusible component capable of diffusing *in vivo* in the gas of the first component (par. 020-023). The association between the two components can be achieved in many ways, including electrostatic binding (see par. 28). Erikson does not teach or suggest use of liposome suspensions as defined by Schneider or mention any interaction between such liposomes and microvesicles.

It is thus apparent that the oil-in-water emulsion disclosed by Eriksen (where the droplets of the emulsion contain a diffusible component at least partially insoluble in and immiscible with water – see par. 0038) is completely different from the liposomes of Schneider (which are dispersed in an aqueous solution and entrap an aqueous solution)

Therefore, the skilled person would not have been prompted to apply the teachings of Eriksen to the disclosure of Schneider, in order to provide an electrostatic binding between the liposomes and the microvesicles of Schneider.

Similarly, Unger does not relate to assemblies comprising two distinct components but rather to a targeted therapeutic delivery system comprising gas-filled microspheres. Thus, the skilled artisan would not have been prompted to apply the teachings of Eriksen to its disclosure. In sum, Applicants submit that the references cannot be combined to suggest modification of Schneider as suggested by the Examiner.

The Cited References Fail to Disclose the Claimed Invention

However, even if one were to assume, for argument's sake, that the references could be combined as proposed, they do not disclose all elements of the claimed invention.

Schneider relates to the combined use of gas-filled microvesicles and of liposomes; the two components can be simply admixed together or "more or less" closely associated to each other. See Schneider, col. 5, lines 45-48. Schneider neither teaches nor suggests the claimed the electrostatic binding between microvesicles and a second component, nor that the dimensions of the second component associated with the microvesicles should be of 100 nm or less.

The cited secondary references fail to remedy these deficiencies. While Eriksen teaches an electrostatic interaction between the particles of an oil-in-water emulsion and microvesicles, it does not disclose that the component associated with the microvesicles shall be of 100 nm or less (to the contrary, as explained above, it teaches that it should be larger than 100 nm). Unger does not relate to assemblies comprising two distinct components but rather to a targeted therapeutic delivery system comprising gas-filled microspheres. Thus, it too fails to teach or suggest a second component associated by electrostatic interaction with a diameter of 100 nm or lower (never mind the advantages associated with such constructs). Consequently, Unger fails to remedy the deficiencies of Schneider and Eriksen.

In sum, even when considered in combination, the cited references fail to disclose each element of the claimed invention and particularly fail to teach or suggest the claimed dimensions of the associated component.

In view of the preceding remarks, it is believed that claims 1-15, 18-24, 27-30, 41-42 and 45 are in condition for allowance. Applicants request rejoinder of claims 35-40, 43 and 44.

If there are any questions remaining as to patentability of the pending claims, Applicants would very much desire to have a telephonic interview. The Examiner is invited to contact Applicants' undersigned attorney at the number below.

No fee is believed to be necessary in connection with the filing of this Response other than the fee for the extension of time. However, if any additional fee is necessary, applicant hereby authorizes such fee to be charged to Deposit Account No. 50-2168.

Favorable action is respectfully requested.

Respectfully submitted,

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